PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

CHARI, Ravi V.J.

Docket No: A8873

Appln. No.: 09/671,995

Group Art Unit: 1643

Confirmation No.: 2588

Examiner: K.A. Canella

Filed: September 29, 2000

For: COMPOSITIONS AND METHODS FOR TREATING CANCER USING IMMUNOCONJUGATES AND CHEMOTHERAPEUTIC AGENTS

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the Pre-Appeal Brief Conference Program, Applicants request a pre-Appeal Brief review of the present application. A Notice of Appeal is submitted herewith along with all required fees.

I. SUMMARY OF THE CLEAR LEGAL ERROR

Claims 93-105, 144, 145, 148 and 149 are pending in the application and these claims are currently rejected under 35 U.S.C. §103(a) in the Final Office Action dated August 9, 2006.

The present claims recite pharmaceutical compositions that provide for synergistic anti-tumor activity, and these synergistic effects are shown in the application as filed and via a Rule 132 Declaration.

The Final Office Action, however, does not consider these synergistic properties, and contends that synergistic properties are not relevant to the non-obviousness of pharmaceutical compositions (see pages 14 and 15 of the Final Office Action). This assertion, and failure to consider the evidence made of record, are clear legal error (*See Knoll Pharmaceutical Co. v. Teva Pharmaceutical USA Inc.*, 70 USPQ2d 1957 (CAFC 2004)) for which a pre-appeal brief review is being requested.

II. THE CLAIMED INVENTION IS A SYNERGISTIC PHARMACEUTICAL COMPOSITION

As stated in the Amendment filed May 17, 2006, cytotoxic drugs that have different mechanisms of killing, that is different cellular targets, are called "mutually exclusive drugs." Most mutually exclusive drug combinations show an additive effect, but some combinations show less or more than the expected additive effect. These combinations are "antagonistic" or "synergistic," respectively.

Antagonistic or synergistic effects are unpredictable and are unexpected experimental findings, as acknowledged by the Examiner at page 16 of the Final Office Action dated August 13, 2004.

The pharmaceutical composition, as defined in independent claim 93, comprises at least one chemotherapeutic agent and at least one immunoconjugate, the immunoconjugate comprising at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof that binds to an antigen expressed by a cancer cell. Claims 94-105, 144, 145, 148, and 149 further define the composition in varying scopes. For example, claim 94 further defines the

chemotherapeutic agent as a taxane compound, an epithilone compound, a platinum compound, an epipodophyllotoxin compound, a campthecin compound, or a mixture of two or more thereof.

The claimed pharmaceutical compositions are synergistic for the treatment of cancer, as is shown in the specification as filed and by the Declaration of Walter A. Blättler submitted May 17, 2006. These synergistic properties are summarized at pages 15-18 of the Amendment filed May 17, 2006.

The Examiner acknowledges at page 14 of the Final Office Action that the claimed compositions have synergistic effects on cancer cells

III. CLAIM REJECTIONS UNDER 35 U.S.C. §103(a)

The Examiner rejects all claims as obvious over various combinations of references that teach the recited cytotoxic drugs individually (see pages 2-14 of the Final Office Action).

The Examiner acknowledges that the art does not teach or suggest that the claimed compositions would be synergistic (see page 14 of the Final Office Action, 3rd and 4th lines from the bottom), but contends that a synergistic property is an intended use entitled to no patentable weight (see page 15 of the Final Office Action).

IV. "OBJECTIVE CRITERIA" SUCH AS UNEXPECTED RESULTS MUST BE CONSIDERED

In the response filed May 17, 2006, Applicants asserted that unexpected properties of claimed products are important considerations in any non-obviousness analysis. See pages 13-15 of the Amendment filed May 17, 2006.

For example, in *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA Inc.*, 70 USPQ2d 1957 (Fed. Cir. 2004), the Federal Circuit considered the propriety of a district court's summary judgment on the basis of obviousness for a claim directed to a pharmaceutical composition comprising hydrocodone and ibuprofen.[1] In *Knoll*, the specification described the "surprising" efficacy of the combination, and additional experimental data was later submitted further demonstrating these synergistic effects.

When the district court refused to consider the evidence of synergistic effects, the Federal Circuit stated (70 USPQ2d at 1960):

> Although the prior art appears to suggest combining an opioid, such as hydrocodone, with various NSAIDs, such as ibuprofen, we conclude, based on the evidence adduced by Knoll, that a genuine factual dispute exists as to the obviousness of the asserted claims which makes summary judgment based on the present record evidence improper. ***There appears to be no record of evidence of prior art teaching or suggesting the enhanced biomedical effect of the combination of hydrocodone and ibuprofen***. The district court refused to consider evidence Knoll presented to show unexpected results using

[1] Claim 2 at issue in *Knoll* read:

> A pharmaceutical composition which comprises hydrocodone or a pharmaceutically acceptable acid addition salt thereof and ibuprofen or a pharmaceutically acceptable acid addition salt thereof in amounts that are sufficient to provide an analgesic effect, the ratio of hydrocodone to ibuprofen being within the range that the administration of a therapeutic amount of said composition to a mammal will provide a greater analgesic effect than the effect obtainable by use of either hydrocodone or a pharmaceutically acceptable acid addition salt thereof or ibuprofen or a pharmaceutically acceptable acid addition salt thereof alone.

> the combination of hydrocodone and ibuprofen, for the reason that the "unexpected benefits or results were discovered after the '252 patent had been issued." Contrary to the district court's perception, the specification expressly acknowledges that the efficacy of the combination is "surprising," in that it provides an analgesic effect greater than that obtained by increasing the dose of either constituent administered alone. In the experimental models in the specification, the analgesia provided by the combination was said to be greater "than that obtained by using either analgesic alone even if the dose is increased." (emphasis added and citations omitted)
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> ***The so-called "objective" criteria must always be considered***, *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), and given whatever weight is warranted by the evidence presented. *See Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1572 (Fed. Cir. 1996) (considering failure of others to find a solution to the problem); *Transmatic, Inc. v. Gulton Indus., Inc.*, 53 F.3d 1270, 1275 (Fed. Cir. 1995) (considering failure of others to make the invention). (emphasis added)

Further, this law, as applied by the Federal Circuit in *Knoll*, is reflected in the current examination guidelines. For example, see MPEP §2141, which states:

> Objective evidence or secondary considerations ***such as unexpected results***, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism by experts are relevant to the issue of obviousness and ***must be considered in every case in which they are present.*** When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

Therefore, under the controlling law and examination guidelines, Applicants' unexpected properties are objective evidence of the non-obviousness of the presently claimed pharmaceutical compositions, and this evidence must be considered by the Patent Office.

The refusal to consider the evidence of unexpected results vis-à-vis the pending claims is clear legal error.

Withdrawal of the Final Office Action is therefore requested.

Respectfully submitted,

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